METAL SALTS OF PARECOXIB AS PRODRUGS OF THE COX-2 INHIBITOR VALDECOXIB FOR THE TREATMENT OF INFLAMMATION, PAIN AND/OR FEVER

FIELD OF THE INVENTION

[0001] The instant invention relates to metal salts useful for treating cyclooxygenase-2 ("COX-2") mediated conditions, to pharmaceutical compositions containing such salts as an active ingredient, to processes for preparing such salts and compositions, to methods of treatment of COX-2 mediated disorders comprising administering such compositions to a subject, and to the use of such compositions in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

[0002] The discovery of selective COX-2 inhibitory compounds has greatly advanced the treatment and/or prophylaxis of conditions in which COX-2 expression modulates such pathology. Such inhibitory compounds provide anti-inflammatory, antipyretic, analgesic and other useful therapeutic effects while minimizing or eliminating adverse side effects known to result from COX-1 inhibition.

[0003] Examples of selective COX-2 inhibitory drugs are set forth in U.S. Patent No. 5,466,823, incorporated herein by reference.

[0004] Other examples of selective COX-2 inhibitory drugs are set forth in U.S. Patent No. 5,892,053, incorporated herein by reference. One such example is celecoxib, also known as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. Celecoxib has a therapeutically and prophylactically useful selective COX-2 inhibitory effect, and has utility in treatment and prevention of COX-2 mediated disorder.

[0005] International Patent Publication No. WO 00/32189, incorporated herein by reference, discloses that celecoxib has a crystal morphology which tends to form long, cohesive needles.

[0006] International Patent Publication No. WO 00/42021, incorporated herein by reference, discloses a solvated crystalline form of celecoxib and a method for desolvation of that crystalline form. The forms of celecoxib generally have a low solubility in aqueous media (about 2 to about 5 μg/mL).

[0007] Valdecoxib (i.e., 4-(5-methyl-3-phenylisoxazol-4-yl) benzenesulfonamide), disclosed in U.S. Patent No. 5,633,272 (incorporated

herein by reference), is among another class of selective COX-2 inhibitory drugs. Valdecoxib is practically water insoluble.

[0008] Parecoxib (i.e., N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide) is described in U.S. Patent No. 5,932,598, incorporated herein by reference. Parecoxib is a prodrug of valdecoxib; parecoxib shows only very low *in vitro* inhibitory activity against COX-1 and COX-2 but upon administration, parecoxib is converted to valdecoxib. Sodium parecoxib ("Na parecoxib"), also disclosed in U.S. Patent No. 5,932,598, is highly water soluble (e.g., 18 mg/mL at pH 7.8) whereas parecoxib free acid ("parecoxib FA") is much less soluble.

[0009] Due to the water solubility of Na parecoxib, a ready-to-use injectable formulation has been developed and commercialized as Dynastat® (TM G.D. Searle & Co.). After intravenous injection of such a formulation, parecoxib rapidly becomes bioavailable. Due to the combined effects of (1) rapid bioavailability and (2) *in vivo* clearance of parecoxib, repeated injections at regular intervals (e.g., daily) are required to maintain maximum effectiveness of parecoxib over the course of treatment.

[0010] Parenteral drug formulations have become a very important component in the arsenal of available drug delivery options, particularly for drugs having analgesic effect. For a wide variety of drugs, parenteral routes of administration (e.g., subcutaneous, intramuscular and intravenous injection), offer numerous benefits over oral delivery. For example, parenteral administration of a drug typically results in attainment of a therapeutically effective blood serum concentration of the drug in a shorter time than is achievable by oral administration. This is especially true of intravenous injection, whereby the drug is placed directly in the bloodstream. Whereas orally ingested drugs tend to result in variable losses in the gastrointestinal tract (e.g., due to metabolism, binding to food and other causes), parenteral administration can result in more predictable blood serum concentrations of a drug. For similar reasons, parenteral administration often permits dose reduction. Parenteral administration is generally the preferred method of drug delivery in emergency situations, and is also useful in treating subjects who are uncooperative, unconscious, or otherwise unable or unwilling to accept oral medication.

[0011] Stable liquid parenteral parecoxib formulations are described in U.S. Patent Application Pub. No. US 2004/0127537 A1.

[0012] It is often desired that a parental drug formulation provides for a longer action compared to other formulations, thereby reducing the frequency of administration. This is especially true when the parental route of administration is invasive painful, emotionally stressful, associated with risk of infection, or requires a visit to a health care provider.

[0013] The healing arts would be advanced if new parecoxib species existed that, when properly formulated, would be useful for a long acting medicament and thereby reduce the number of injections or the difficulties associated with oral medications in certain situations.

SUMMARY OF THE INVENTION

[0014] There is now provided in the instant invention a selective COX-2 inhibitory compound comprising a magnesium salt of parecoxib useful for treating a subject with a COX-2 mediated disorder.

[0015] It should be understood that the term "treating a subject with a COX-2 mediated disorder" is mean to embrace prophylactic administration of the instant compound to a subject with a likelihood of developing a COX-2 mediated disorder. Also, as used herein, the term "COX-2 mediated disorder" is meant to embrace conditions where COX-2 activity underlies a pathology or an unwelcome physical effect.

[0016] In one embodiment, the magnesium salt of parecoxib is magnesium diparecoxib ("Mg diparecoxib").

[0017] In one embodiment, the Mg diparecoxib of the present invention is crystalline. In another embodiment, the Mg diparecoxib crystals are non-needle-like. By way of example, the non-needle-like crystals of the present invention are cuboidal or polygonal.

[0018] In another embodiment, Mg diparecoxib of the present invention is in a pharmaceutical composition also comprising at least one excipient. Such dosage forms are useful for oral ingestion as a tablet, capsule, suspension, and the like.

[0019] In another embodiment, the pharmaceutically acceptable dosage form of the instant invention is a composition suitable for parenteral administration.

[0020] In another embodiment, the parenterally administrable composition of the instant invention is suitable for depot administration.

[0021] In another embodiment, Mg diparecoxib is in the form of a pharmaceutical composition further comprising a second active ingredient.

[0022] In another embodiment is provided a compound having the structure $MX^1(X^2)_n$ wherein M is a metal cation selected from the group consisting of Ca^{2+}, Zn^{2+}, and K^+; X^1 is parecoxib anion; X^2 is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion; and n is 0 when M is K^+ and n is 1 when M is Ca^{2+} or Zn^{2+}.

[0023] In another embodiment, the instant invention provides a depot formulation of a parecoxib salt that, when administered as a depot, results in therapeutic levels of valdecoxib. Such a parecoxib salt is selected from Mg diparecoxib, zinc diparecoxib ("Zn diparecoxib"), calcium diparecoxib ("Ca diparecoxib"), potassium parecoxib ("K parecoxib"), and Na parecoxib.

[0024] In another embodiment, the instant invention provides a depot composition of valdecoxib that, when administered as a depot to a subject in need thereof, results in therapeutic levels of valdecoxib.

[0025] In another embodiment, a depot composition of the instant invention wherein, upon injection into at least one parenteral site of a subject, provides at least one of the following:

[0026] (a) a therapeutic level of valdecoxib within about 10, alternatively about 5, or alternatively about 3 hours after depot administration;

[0027] (b) a therapeutic level of valdecoxib for at least about 2, alternatively for at least about 3, or alternatively for at least about 4 days;

[0028] (c) a time to reach a maximum blood serum concentration (T1/2max) of valdecoxib that is not greater than about 20, alternatively not greater than about 10, or alternatively not greater than about 3 hours after administration.

[0029] This invention also provides a method for preparing Mg diparecoxib, the method comprising an *in situ* crystallization method.

[0030] This invention also provides a method for preparing Mg diparecoxib, the method comprising the step of precipitating Mg diparecoxib from parecoxib FA, for example, by reacting $MgOH_2$ with solubilized parecoxib FA.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] FIG. 1 shows the UV absorbance spectra of the supernatants from *in situ* crystallization of the parecoxib salts as described in Example 1.

[0032] FIG. 2 shows a 600X magnification of Ca diparecoxib crystals.

[0033] FIG. 3 shows a 600X magnification of Mg diparecoxib crystals.

[0034] FIG. 4 shows time-dependant solubilization of Mg diparecoxib, parecoxib FA, and valdecoxib suspensions in a dissolution apparatus.

[0035] FIG. 5 shows microscopy of parecoxib FA compositions formed as described in Example 4.

[0036] FIG. 6 shows microscopy of Mg diparecoxib compositions formed as described in Example 4.

[0037] FIG. 7 shows microscopy of valdecoxib compositions formed as described in Example 4.

[0038] FIG. 8 shows plasma levels of valdecoxib after suspension of Example 4 were injected into dogs.

[0039] FIG. 9 shows cumulative input rate of valdecoxib from Example 5.

[0040] FIG. 10 shows plasma valdecoxib concentration with time following Mg diparecoxib depot administration to dogs.

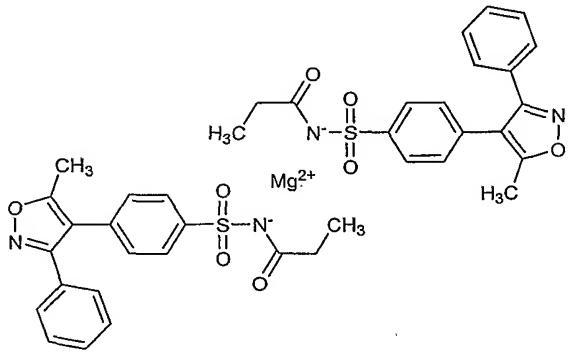
[0041] FIG. 11 shows theoretical plasma valdecoxib levels that are predicted to follow Mg diparecoxib depot administration to humans.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0042] In one embodiment of the present invention is provided a magnesium salt of parecoxib having the structure MgX^1X^2, wherein X^1 is parecoxib anion and X^2 is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion. Suitable pharmaceutically acceptable anions include, but are not limited to, chloride, bromide, sulfate, phosphate, nitrate, acetate, propionate, succinate, glycolate, stearate, lactate,

malate, tartrate, citrate, ascorbate, glutamate, benzoate, salicylate, methanesulfonate, and toluenesulfonate.

[0043] In one embodiment, the magnesium salt of parecoxib is substantially in the form of Formula I



[0044] I

[0045] and is referred to herein as Mg diparecoxib. The term "substantially in the form of Formula I" is meant to embrace molecular forms wherein the parecoxib anion to magnesium cation molar ratio is between about 1.5 and about 2.5, preferably about 2.

[0046] In one embodiment, Mg diparecoxib is crystalline. In a preferred embodiment, magnesium salts of the present invention are non-needle-like crystals, for example, cuboidal or polygonal crystals.

[0047] In one embodiment, the Mg diparecoxib is of a form having a relatively low surface area to volume ratio (especially when compared to needle-like crystals). The term "relatively low," in this context, means a surface area to volume ratio less than about 48 μm^{-1}, preferable less than about 24 μm^{-1}, more preferably less than about 12 μm^{-1}.

[0048] In another embodiment, in the absence of milling or sonication or the like, the Mg diparecoxib crystals have an average particle size, using a Horiba Particle Sizer, of about 40 μm. In the absence of milling or sonication or the like, the crystals of the present invention have a D_{90} (by mass) of less than about 100 μm, preferably less than about 60 μm, more preferably about 40 μm (based upon the longest length of the crystal).

[0049] After 1 min sonication of an alternative embodiment, the crystals have an average particle size, using a Horiba Particle Sizer, of about 20 μm. Alternatively, such crystals have a D_{90} (by mass) of less than about 60 μm,

alternatively less than about 40 μm, alternatively about 20 μm (based upon the longest length of the crystal).

[0050] In another embodiment is provided a compound having the structure $MX^1(X^2)_n$ wherein M is a metal cation selected from the group consisting of Ca^{2+}, Zn^{2+}, and K^+; X^1 is parecoxib anion; X^2 is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion; and n is 0 when M is K^+ and n is 1 when M is Ca^{2+} or Zn^{2+}.

[0051] Two exemplary methods are contemplated herein to prepare Mg diparecoxib. In one method, Mg diparecoxib is precipitated from parecoxib FA, which may be prepared as described in U.S. Patent No. 5,932,598. Next, parecoxib FA may be suspended or dissolved in a liquid. For example, a 75 mM suspension of parecoxib FA may be made in ethanol. Additionally, a magnesium salt (e.g., $Mg(OH)_2$, $MgCl_2$ or Mg) may be suspended or dissolved in a second liquid. For example, a 55 mM suspension of $Mg(OH)_2$ may be made in ethanol. Next, the suspension or solution of parecoxib FA and a magnesium salt may be combined. For example, three parts of the aforementioned 75 mM parecoxib FA suspension may be combined with two parts of the aforementioned 55 mM $Mg(OH)_2$ suspension. In one alternative, in the combined suspension or solution, the molar ratio of parecoxib anion to the magnesium cation is 2 to 1, alternatively the molar ratio is more than about one to one and less than about four to one. Next, the combination may be agitated (e.g., stirred) for a period of time (e.g., for 10 minutes or more). During this agitation period, magnesium salt of parecoxib will precipitate. The precipitates may be collected, for example, by centrifugation or by evaporating the ethanol (e.g., *in vacuo*). Optionally, the crystals may be dried (e.g., at high vacuum).

[0052] Magnesium diparecoxib may alternatively be prepared by *in situ* crystallization. Sodium parecoxib, prepared as described in U.S. Patent No. 5,932,598, may be dissolved in a liquid. For example, the liquid can be water, and optionally the liquid may be buffered. By way of example, Na parecoxib may be dissolved in 15 mM Tris adjusted to a slightly basic pH (e.g., pH 8) to avoid formation of valdecoxib at a useful concentration (e.g., at 10-40 mg parecoxib FA equivalents/mL) to form a solution. This solution may be combined with a concentrated magnesium salt solution (e.g., $MgCl_2$ or $MgSO_4$). Optionally, the parecoxib solution and the magnesium salt solution may be combined such that

the molar ratio of parecoxib anion to cation is greater than about 1, optionally greater than about 1.5 or greater than about 2. Next, the combination may be agitated (e.g., stirred) for a period of time (e.g., for about one to about 30 minutes or for overnight). During this agitation period, the magnesium salt of parecoxib will precipitate. After the agitation period, Mg diparecoxib precipitates may be separated from the solution, for example, by centrifugation or filtration, as described above.

[0053] Other variations for preparing Mg diparecoxib are set forth below by way of working examples. A skilled artisan can understand that, based upon the disclosure herein, Ca diparecoxib, Zn diparecoxib, and K parecoxib can similarly be made. For example, K parecoxib can be made by adding KOH to parecoxib FA by the procedure taught above.

[0054] In another embodiment is provided a pharmaceutical compositions comprising Mg diparecoxib and one or more pharmaceutically acceptable excipients. Based upon the disclosure herein, one of skill in the art can select one or more pharmaceutically acceptable excipients selected according to the desired route of administration, desired plasma levels of valdecoxib, and desired duration of therapeutic levels of circulating valdecoxib.

[0055] In one embodiment, the instant composition comprises Mg diparecoxib in an amount of at least about 1% by weight of the total composition weight, alternatively at least about 10% or at least about 20% by weight.

[0056] These pharmaceutical compositions may be prepared in an oral dose unit in the form of discrete solid articles such as tablets, pills, hard or soft capsules, lozenges, sachets or pastilles; alternatively the composition can be in the form of a substantially homogeneous flowable mass, such as a particulate, powder, or granular solid or a liquid suspension, from which single dose units are measurably removable. Alternatively, these pharmaceutical compositions are in a form suitable for parenteral administration. The term "parenteral administration" herein encompasses injection and/or infusion of a composition into or through the skin of a subject, and includes, without limitation, intradermal, subcutaneous, intramuscular, intravenous, intramedullary, intra-articular, intraperitoneal, intralymphoid, intrasynovial, intraspinal, intrathecal, subdural, and intracardiac administration. Any known device useful for parenteral injection or infusion of drugs can be used to effect such administration.

[0057] Parenterally-deliverable embodiments of the instant invention satisfy one or more, optionally three or more, optionally five or more, optionally seven or more, or optionally nine or more of the following criteria: sterility, low endotoxin level, defined particle size range, no "caking" during shelf life, easy redispersion with mild shaking, slow rate of settling after redispersion, homogeneity of suspension after redispersion, syringeable and injectable through narrow gauge needle, formulation isotonicity and pH close to physiologic range, physical particle stability (e.g., no polymorphism or crystal growth), and chemical stability.

[0058] Parenterally deliverable compositions of the instant invention comprise Mg diparecoxib in a therapeutically effective amount. The compositions may also comprise one or more of the following: a parenterally acceptable buffer for adjusting and/or maintaining pH of the composition; an isotonicity agent; a suspending agent to reduce undesired settling out of Mg diparecoxib in liquid compositions; and a solubilizing agent.

[0059] Where it is desired to have the Mg diparecoxib in a soluble composition (e.g., for intravenous administration), a solubilizing agent can comprise, for example, at least one cyclodextrin. Suitable cyclodextrins include α-cyclodextrins and β-cyclodextrins (also referred to herein as β-CD). Preferably, the cyclodextrins are β-cyclodextrins. Among these optional cyclodextrin derivatives are those wherein the C_{2-6} alkylene is a C_3 or C_4 alkylene. Also among these optional cyclodextrins is sulfoalkylether β-cyclodextrin, for example, sulfobutylether-β-cyclodextrin having an average substitution of about 4 to about 8 and preferably about 5 to about 7, for example, about 6.4 sulfobutyl ether linkages (i.e., sulfobutyl ether$_{6.4}$-β-cyclodextrin).

[0060] The composition of the instant invention can comprise at least one non-aqueous solubilizing agent such as a polyethylene glycol, ethanol, dimethylacetamide (DMAC), a propylene glycol, and mixtures thereof.

[0061] Compositions of the instant invention optionally comprise a isotonicity agent, for example, NaCl, sorbitol, mannitol, dextrose, polyethylene glycols ("PEGs"), phosphate buffers, methyl and propyl parabens, polyethylene glycols, carboxymethylcelluloses, alginate, polyvinyl pyrrolidones, or polysorbates.

[0062] As used herein, "isotonic" means that the osmolarity of the solution is substantially the same as the physiological osmolarity (i.e., the tonicity or osmotic pressure of the solution is similar to that of blood).

[0063] In one parenterally deliverable composition of the instant invention, the composition is in powder form. The powder form is optionally reconstitutable in a parenterally acceptable solvent liquid, optionally an aqueous liquid, to form a solution suitable for injection.

[0064] The parenterally deliverable composition in powder form can be prepared by a process comprising a step of removing water from an aqueous solution (by, for example, lyophilization) comprising Mg diparecoxib and optionally one or more buffers, a isotonicity agent, and a suspending agent to form a readily reconstitutable powder.

[0065] In one embodiment, the invention is an article of manufacture comprising a sealed vial having contained therewithin a sterile, parenterally deliverable composition of the instant invention in powder form. One skilled in the art can recognize that such an article of manufacture can optionally contain a useful volume of a solvent (e.g., water) sequestered from the powder form in a compartment that allows mixing of the water and the powder form before use without opening the sealed vial.

[0066] In another embodiment, the invention is an injectable solution prepared by reconstitution of the composition.

[0067] In another embodiment, the invention is an article of manufacture comprising a sealed vial having contained therewithin a unit dosage amount of the composition in a sterile condition.

[0068] In one embodiment, the parenterally deliverable composition of the instant invention is suitable for depot administration. Such a depot administration preferably delivers a therapeutically effective dose for a sustained period of time, for example, at least about two days, optionally at least about three days, optionally at least about four days, or optionally at least about five days.

[0069] As used herein, a "depot" is a pharmaceutical composition containing a therapeutically active agent that is suitable for administration by implantation or injection into a local site that results in a gradual release (for example, release over a few hours or a few days) of the active agent into

circulation. Release of the active agent is modulated by the nature of the site injected or implanted, the solubility of the active agent, and the precise composition of the depot.

[0070] As used herein, "depot administration" means the administration by implantation or injection, for example, subcutaneous, intramuscular, intradermal, and intra-articular administration. Thus, a depot administration is to be contrasted with, for example, an intra venous injection that results in rapid systemic delivery of the active agent (for example, within minutes of injection).

[0071] The depot compositions of the instant convention can contain Mg diparecoxib and a means for stabilizing and/or controlling solubilization rate of the Mg diparecoxib. Such stabilizing and/or controlling means can be selected from suitable polymeric or hydrophobic materials or ion-exchange resins. By way of example, an emulsion can be produced from Mg diparecoxib using an acceptable oil to stabilize or control release of Mg diparecoxib.

[0072] Pharmaceutical compositions of the instant invention are characterized by at least one feature selected from the group consisting of steady extended release, useful release rate, minimal pain on injection, no local toxicity due to depot, a duration of action correlated with dose, and a correlation between *in vitro* and *in vivo* release.

[0073] Depots of the instant invention contain Mg diparecoxib at a concentration useful for parenteral administration that results in a therapeutic level of valdecoxib. Such a useful concentration is about 40 to 500 mg/mL, for example, about 80 mg/mL to about 280 mg/mL.

[0074] Another embodiment of the present invention is a method of administering Mg diparecoxib in depot formulation Such a method delivers an amount of Mg diparecoxib in an amount of about 40 mg to about 500 mg, optionally 60 mg to about 400 mg or optionally about 80 mg to about 280 mg.

[0075] In another embodiment, the depot composition of the instant invention contains a second therapeutically active agent. As used herein, the term "active agent" may refer to a drug or a prodrug. In one embodiment, the second active agent is an analgesic, an anti-pyretic, and/or an anti-inflammatory compound. In a particular embodiment, the second active agent is a selective COX-2 inhibitor; optionally the selective COX-2 inhibitor is a valdecoxib prodrug or valdecoxib. In a particular embodiment, the second active agent delivers a

therapeutic level of valdecoxib more rapidly than does Mg diparecoxib in the same embodiment. Optionally, such a composition comprises Mg diparecoxib and a second active agent in an amount such that, when administered as a depot, therapeutic levels of circulating valdecoxib attain the predicted therapeutic need over a period of two or more days. Examples of selective COX-2 inhibitors useful as the second active agent are valdecoxib, celecoxib, rofecoxib, etoricoxib, lumiracoxib, and parecoxib, or salts thereof.

[0076] Examples of such embodiments are a dosage form comprising Mg diparecoxib and Na parecoxib; Mg diparecoxib and Ca diparecoxib; Mg diparecoxib and Zn diparecoxib; Mg diparecoxib and K parecoxib; and Mg diparecoxib and valdecoxib.

[0077] As disclosed herein, physicochemical properties of salts of the present invention (e.g., Mg diparecoxib, Ca diparecoxib, Zn diparecoxib, and K parecoxib) and valdecoxib contribute, in part, to a dosage form with different pharmacokinetic properties. Such pharmacokinetic properties include, by way of example, dissolution rate, bioabsorption rate, time to reach maximum concentration (T_{max}), the duration of time that therapeutic (or other) levels are sustained; the terminal half-life ($T_{1/2}$); and maximum concentration (C_{max}).

[0078] Based upon such properties as disclosed herein, a skilled artisan is able to combine compounds of the present invention in absolute and relative amounts such that, when formulated and administered as a depot, any desired circulating levels of valdecoxib can be achieved, even if such desired levels predictably change with time following administration.

[0079] By way of example, in certain circumstances it may be desired to rapidly achieve a first therapeutic level, for example, 75 ng valdecoxib/mL plasma. It can be desirable to sustain such first therapeutic level for a certain first period of time, for example, two days. Moreover, in the same such circumstance after the first period of time, it can be desired to achieve a second therapeutic level for a second period of time, for example, 25 ng valdecoxib/mL plasma for four days. Moreover, in the same such circumstance after the second period of time, it can be desired to achieve a third valdecoxib level for a third period of time. Such third level can be a changing level (for example, 25 ng valdecoxib/mL plasma) decreasing to 0 ng valdecoxib/mL plasma over the course of the third period of time (for example, two days).

[0080] Examples of situations where the therapeutic need could change with time are conditions wherein there is a rapid onset of pain and conditions of acute pain, where the physiologic healing process is expected to reduce the therapeutic need with time. Specific instance include, by way of example, oral surgery, surgical removal of a tissue (e.g., biopsy, appendectomy, etc.), vaccination, cosmetic surgery, etc.

[0081] Compositions of the invention are useful in subjects for treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such composition possess the additional benefit of having significantly less harmful side effects than compositions of conventional NSAIDs that lack selectivity for COX-2 over COX-1. In particular, compositions of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation, including upper gastrointestinal ulceration and bleeding, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example, in subjects with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in subjects prior to surgery or subjects taking anticoagulants.

[0082] Compositions of the instant invention are useful in treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated. More preferred uses include treatment for an acute condition (e.g., a condition where treatment is need for a period of several days to several weeks).

[0083] Compositions of the instant invention are useful in treatment of pain, including but not limited to perioperative pain, postoperative pain, post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, dental pain, muscular pain, and pain resulting from cancer.

[0084] It is now disclosed that a single administration of a depot composition of the instant invention within one week prior to surgery reduces perioperative pain (i.e., pain associated with the surgical procedure itself and the more intense and/or acute pain following the surgery) and reduces post operative pain (i.e., pain following the more intense and/or acute pain phase). It should be

understood that the distinction between late preoperative pain phase and early post-operative pain phase is sometime unclear or non-existent. Examples of such a useful pre-operative injection regimen is an injection minutes prior to surgery, optionally within 24 hours before surgery, optionally within 48 hours before surgery, or optionally within one week before surgery.

[0085] It has further been the surprising discovery that a single administration of a depot composition of the instant invention within the aforementioned useful pre-operative injection regimen reduces the need for administration of an opiate for analgesia.

[0086] Compositions of the instant invention are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, radiation damage, and trauma following surgical and dental procedures.

[0087] Contemplated compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

[0088] Such compositions are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

[0089] Such compositions of the instant invention are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial

cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such compositions can also be used to treat fibrosis that occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such compositions can be used to prevent polyps from forming in subjects at risk of FAP.

[0090] Subjects undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine effectiveness of therapy. Continuous analysis of data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective doses are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the composition exhibiting satisfactory effectiveness is administered, and so that administration is continued only for so long as is necessary to successfully treat the condition or disorder.

[0091] Parecoxib salts of the instant invention (e.g., Mg diparecoxib, Zn diparecoxib, Ca diparecoxib, and K parecoxib) when administered parenterally to a human subject, are rapidly and completely converted to valdecoxib. Therefore, a therapeutically effective dose of parecoxibs of the instant invention is one that delivers a therapeutically effective circulating dose of valdecoxib. By way of example, therapeutic levels typically are at least about 20 ng/mL plasma, for example, about 25 to about 75 ng/mL.

[0092] Therapeutic methods of the instant invention further include combination therapies of parecoxib or a composition of the invention with one or

more drugs selected from opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e., non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, e-acetamidocaproic. acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole

salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone HCl, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine HCl, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine HCl, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition, Therapeutic Category and Biological Activity Index, ed. S. Budavari (1996), pp. Ther-2 to Ther-3 and Ther-12 (Analgesic (Dental), Analgesic (Narcotic), Analgesic (Non-narcotic), Anti-inflammatory (Non-steroidal)).

[0093] Therapeutic methods of the instant invention further include combination therapies of the parecoxib salts of the instant invention with one or more antineoplastic agents (e.g., antineoplastic topoisomerase II inhibitors, antineoplastic antimicrotubule agents, antineoplastic alkylating agents, antineoplastic antimetabolites, and antineoplastic topoisomerase I inhibitors). Antineoplastic topoisomerase II inhibitors can, by way of example, be

anthracycline compounds (e.g., doxorubicin, daunomycin, methoxy-morpholino-doxorubicin, epirubicin idarubicin and nemorubicin); anthraquinone compounds (e.g., mitoxantrone and losoxantrone); and podophillotoxine compounds (e.g., etoposide and teniposide). Antimicrotubule agents can, by way of example, be taxane compounds (e.g., paclitaxel and docetaxel) and vinca alkaloids (e.g., vinblastine and vinorelbine). Alkylating agents can, by way of example, be cyclophosphamide, ifosfamide, chlorambucil, and melphalan. Antineoplastic antimetabolite agents can, by way of example, be 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate. Antineoplastic topoisomerase I inhibitors can, by way of example, be topotecans, irinotecans, and 9-nitrocamptothecin.

[0094] As used herein, the term "subjects", as objects of treatment with compositions of the instant invention, means animals. Preferably such animals are humans or companion animals, exotic animals, farm animals, and the like, particularly mammals. Other preferred animals are horses, dogs and cats with a COX-2 mediated disorder.

[0095] As used herein, the term "*in vivo* administration" means administration to a subject by oral or parenteral route.

[0096] The instant invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising parenteral administration of a composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder is determined in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely.

[0097] Compounds of the present invention are salts of parecoxib, a prodrug of valdecoxib, which is a selective COX-2 inhibitor. The terms "cyclooxygenase-1" and "COX-1" used interchangeably herein refer to the constitutive isoform of the enzyme cyclooxygenase. The terms "cyclooxygenase-2" and "COX-2 as used interchangeably herein refer to the inducible isoform of the enzyme cyclooxygenase. As used herein, the terms "cyclooxygenase-2 selective inhibitor" and "COX-2 selective inhibitor" refer to a compound that inhibits COX-2 more than it inhibits COX-1 in an *in vitro* recombinant enzyme

assay. The term "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" refers to any compound which inhibits the COX-2 enzyme, without regard to the extent to which it inhibits COX-1. Especially suitable as COX-2 selective inhibitors useful in the present invention are those compounds that have a COX-2 IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of COX-2 inhibition over COX-1 inhibition of at least 50 or alternatively, at least 100. In another embodiment, the COX-2 selective inhibitor compounds have a COX-1 IC_{50} of greater than about 1 μM or alternatively, greater than 10 μM.

EXAMPLES

Example 1: Preparation of Mg diparecoxib, Zn diparecoxib, Ca diparecoxib, and K parecoxib

[0098] Magnesium diparecoxib, Zn diparecoxib, Ca diparecoxib, and K parecoxib were prepared using *in situ* crystallization. Briefly, solutions of Na parecoxib were prepared in water for injection ("WFI") at 10 mg/mL. Salt solutions were prepared in WFI using KCl, $CaCl_2$, $MgCl_2$, or $ZnCl_2$. Stoichiometric excess of the chloride salt solutions were added individually to Na parecoxib solutions, and WFI was added to a control solution of Na parecoxib. After 24 hours, precipitate was visually observed in the vials to which $CaCl_2$, $MgCl_2$, and $ZnCl_2$ were added. There was no precipitate in the vials to which either KCl or H_2O was added.

[0099] The supernatant from each vial was sampled and analyzed by UV absorbance after appropriate dilution to detect the concentration of parecoxib in solution. The solutions from the vials containing calcium, magnesium or zinc ions showed reduction in the concentration of parecoxib, indicating that the precipitates observed were those of parecoxib salts formed with the respective counterions. Thus, the amount of parecoxib in the supernatant was indirectly proportional to the water solubility of the parecoxib salt. There was no loss of parecoxib concentration in the vials where no precipitate was observed (i.e., where KCl or H_2O was added).

[00100] The UV absorbance spectra (Figure 1) indicated that the lowest levels of parecoxib in the supernatants were in the vials where $CaCl_2$ or $MgCl_2$ were added. However, most of the parecoxib remained in solution after addition

of $ZnCl_2$, indicating that Zn diparecoxib has greater aqueous solubility as compared to the calcium or magnesium salts of parecoxib.

[00101] From the UV absorbance data shown in Figure 1, the relative solubilities of the salts tested were estimated to be in the following descending order: Na parecoxib ≈K parecoxib > Zn diparecoxib > Ca diparecoxib > Mg diparecoxib.

Example 2: Preparation of Mg diparecoxib and Ca diparecoxib

[00102] Since Ca diparecoxib and Mg diparecoxib exhibited the lowest solubilities of the parecoxib salts examined in Example 1, these two salt forms of parecoxib were selected for further investigation.

[00103] A series of compositions of Ca diparecoxib and Mg diparecoxib were prepared by *in situ* crystallization, starting from solutions of Na parecoxib. A slightly basic pH was selected for *in situ* crystallization in order to avoid formation of parecoxib FA, and to obtain compositions with near physiologic pH.

[00104] Sodium phosphate was tested for compatibility with the $CaCl_2$ and $MgCl_2$ reagents. However, under the conditions tested, in the absence of parecoxib, poorly soluble salts of calcium phosphate and magnesium phosphate, respectively, were formed. However, when the cationic buffer Tris was tested, no precipitate formed in the absence of parecoxib. This was believed to be due, in part, to the fact that the cationic buffer cannot form ionic salts with calcium or magnesium cations. Therefore, Tris was selected as the buffer reagent for the next experiment.

[00105] Calcium diparecoxib and Mg diparecoxib compositions were prepared by *in situ* crystallization from Na parecoxib at approx 40 mg/mL in 15 mM Tris buffer (~ pH 8). Four stoichiometries of Ca^{2+} and Mg^{2+} were tested. Calculated volumes of 1M $CaCl_2$ and $MgCl_2$ salt solutions were added to buffered solutions of Na parecoxib to provide 0.5, 1, 2, and 4 molar equivalents of Ca^{2+} and Mg^{2+} relative to parecoxib, as per Table I. Control compositions were also prepared wherein the salt solutions were added to Tris buffer with no parecoxib present, or where water was added to Na parecoxib solution instead of salt. Visible precipitation was observed in each case soon after addition of the salt solutions to Na parecoxib solutions, and no precipitation was observed for the

control compositions. The compositions were allowed to stir overnight before further analysis.

[00106] After overnight stirring, visual observations were made. All the Ca diparecoxib and Mg diparecoxib compositions were white aqueous suspensions. Some turbidity also developed in the Na parecoxib control composition after overnight stirring. Without limiting the scope of the invention, this turbidity was believed to result from the fact that Na parecoxib is known to form supersaturated solutions, and its solubility is highly dependent on ionic and pH conditions. Aliquots of all the compositions were obtained and centrifuged to suspend any particles. The clear supernatants were analyzed for observed pH and UV absorbance (Table I). Additional aliquots of the suspensions were observed by optical microscopy under polarized light. Representative micrographs are shown in Figures 2 and 3.

Table I. Composition Stoichiometry and Observations

Stoichiometry (parecoxib : cation)		**pH**	**Absorbance[1]**	
			1850x dilution	**100x dilution**
Control (1 : 0 cation)[2]		8.2	1.010[3]	N/A[4]
Ca^{2+}	1 : 0.5	8.0	0.508	N/A
	1 : 1	7.9	0.085	1.541
	1 : 2	7.8	0.033	0.612
	1 : 4	7.7	0.023	0.434
	0 : 4[5]	7.7	0.001	0.001
Mg^{2+}	1 : 0.5	8.0	0.493	N/A
	1 : 1	7.9	0.027	0.507
	1 : 2	7.9	0.012	0.223
	1 : 4	7.8	0.007	0.108
	0 : 4[5]	7.8	0.001	0.000

1: at 245 nm
2: turbid liquid
3: For comparison with absorbance of parecoxib control, absorbance of freshly prepared Na parecoxib composition (without turbidity) was 1.019
4: Not analyzed
5: clear solution

[00107] The UV absorbance results in Table I demonstrate that at every stoichiometry tested, greater amounts of parecoxib salt precipitated out due to addition of magnesium cations as compared to addition of calcium cations. For example, in the case of Ca diparecoxib 1:1 composition, about 8.5% of the starting parecoxib remained in aqueous solution. In comparison, the

corresponding percentage for the Mg diparecoxib 1:1 composition was 2.7% (about 1 mg/mL), suggesting that about 97% of the parecoxib in this composition was now present as suspended particles. These observations confirmed the initial result which suggested that Mg diparecoxib has lower solubility compared to the calcium salt.

[00108] Optical microscopy of the suspension compositions showed that needle like crystals were formed for Ca diparecoxib (Fig 2), whereas Mg diparecoxib crystals exhibited cuboidal/polygonal morphology (Fig 3). The latter crystal morphology is relatively more desirable for several reasons: reduced surface area for dissolution (leading to slow release), easier syringeability, and reduced likelihood of pain at injection site.

Example 3: *In vitro* solubility of Mg diparecoxib

[00109] *In vitro* solubility of dry powder of Mg diparecoxib was determined in various dissolution media and compared to solubility of parecoxib FA and valdecoxib. As shown in Table II, solubility of dry powder of Mg diparecoxib in acidic media was similar to parecoxib FA, solubility of Mg diparecoxib in phosphate buffer at near-physiologic pH was substantially higher than that of parecoxib FA.

Table II

Dissolution Medium	mg/L medium		
	Valdecoxib	Parecoxib FA	Mg diparecoxib
0.1N HCl	97	39	39
0.01N HCl	197	59	72
0.01N HCl + 0.1% SDS	243	292	380
0.5% SDS	1,180	940	19,200
1% Bile salts	297	5,170	19,600
pH 6.8 phosphate buffer	90.7	6,150	11,500
pH 7.4 phosphate buffer	89.5	14,500	19,400

[00110] The time-dependant solubilization of a Mg diparecoxib suspension in a pH 6.8 phosphate buffer was examined by adding 1.5 mL of a 40 mg/mL suspension to 98.5 mL of buffer in a dissolution apparatus. At times indicated in Table III, suspension samples were analyzed for soluble drug content. As shown in Table III and Figure 4, Mg diparecoxib surprisingly revealed a very rapid solubilization, a plateau for about 20 hours, and then a gradual

increase in solubilization with time. This gradual solubilization phase roughly paralleled parecoxib FA, but in an amount substantially higher than the free acid.

Table III

Time (h)	mg/mL		
	Valdecoxib	Parecoxib FA	Mg diparecoxib
0.033	0.008	0.033	0.285
0.083	0.012	0.057	0.283
0.250	0.015	0.089	0.290
0.500	0.017	0.116	0.293
1.000	0.018	0.135	0.299
2.000	0.018	0.164	0.296
17.000	0.021	0.210	0.296
24.000	0.014	0.232	0.345
89.000	0.025	0.309	0.397

Example 4: Compositions of Mg diparecoxib, parecoxib FA, and valdecoxib

[00111] Magnesium diparecoxib, parecoxib FA, and valdecoxib were formulated into pharmaceutically acceptable suspensions set forth in Table IV. The starting material for valdecoxib was prepared by *in situ* crystallization using controlled addition of a valdecoxib/PEG 400 solution to a sterile filtered aqueous buffer (set forth below). The starting material for parecoxib FA was prepared by *in situ* crystallization by controlled addition of hydrochloric acid to a sterile filtered solution of Na parecoxib. The starting material for Mg diparecoxib composition was prepared by *in situ* crystallization by controlled addition of $MgCl_2$ (at a slight excess) to a sterile filtered solution of Na parecoxib.

Table IV

Active agent; concentration	Excipients
Valdecoxib; 34 mg/mL	34 mg/mL Na_3PO_4: 10 mM, pH 7.5 Mannitol: 5% w/v PEG 400: 20% w/v
parecoxib FA; 40 mg/mL	40 mg/mL NaOAc: 10 mM, pH 5 Mannitol: 5% w/v PEG 3350: 5% w/v NaCl: ~100 mM Polysorbate 80: 0.05% v/v

Mg diparecoxib; 42 mg/mL	42 mg/mL Tris HCl: 10 mM, pH 7.5 Mannitol: 5% w/v $MgCl_2$: 5 mM NaCl: ~100 mM

[00112] The parecoxib FA, Mg diparecoxib, and valdecoxib crystals formed in the compositions above were analyzed by microscopy and shown in Figures 5, 6, and 7 (respectively). Parecoxib FA crystals were cuboidal or polygonal. Average particle size (using Horiba Particle Sizer) was about 28 µm. After 1 min sonication, average particle size was about 16 µm. Magnesium diparecoxib crystals were cuboidal or polygonal. Average particle size (using Horiba Particle Sizer) was about 40 µm. After 1 min sonication, average particle size was about 20 µm. Thus, the crystals of Mg diparecoxib have the surprising result of having properties especially favorable for depot formulation, that is, reduced surface area for dissolution (leading to slow release), easier syringeability, and less pain at injection site. Valdecoxib crystals were cuboidal or polygonal. Average particle size (using Horiba Particle Sizer) was about 75 µm. After 1 min sonication, average particle size was about 18 µm.

Example 5: Screening of Mg diparecoxib compositions

[00113] Ten Mg diparecoxib suspension compositions were prepared at a 20 mL volume and at 40 mg/mL concentration to evaluate effect of different excipients, as described in Table V. The compositions were prepared by *in situ* crystallization, starting from solutions of Na parecoxib in Tris buffer. Two different reagents ($MgCl_2$ and $MgSO_4$) were evaluated as source of magnesium ions for the *in situ* salt formation. Five compositions were prepared with each of these two reagents, and with various excipients.

Table V. Mg diparecoxib compositions

Composition	Prepared from	Excipients
A	$MgCl_2$	10 mM Tris buffer
B	$MgSO_4$	
C	$MgCl_2$	10 mM Tris buffer, 0.9% NaCl
D	$MgSO_4$	
E	$MgCl_2$	10 mM Tris buffer, 0.9% NaCl, 0.05% Polysorbate 80
F	$MgSO_4$	

Composition	Prepared from	Excipients
G	$MgCl_2$	10 mM Tris buffer, 5% mannitol
H	$MgSO_4$	
I	$MgCl_2$	10 mM Tris buffer, 5% mannitol, 3% PEG 3350
J	$MgSO_4$	

[00114] All the compositions gave white suspensions were obtained. During preparation, nucleation of the compositions was necessary with a few μL of a Mg diparecoxib composition prepared separately at a smaller 5 mL scale (no nucleation was necessary at the smaller scale).

[00115] The suspension compositions were analyzed by pH, UV absorbance in supernatant, redispersability, syringeability, sedimentation volume, dose transfer accuracy and optical microscopy. A summary of the results is provided in Table VI. For all compositions in Table VI, equivalent stoichiometry (parecoxib : Mg) is 1 : 1.1; molar stoichiometry (parecoxib : Mg) is 1 : 0.55; syringeability at ~40 h is pass; and microscopy (μL) is ~2-10. The pH of compositions A, C, E, G, and I was 7.6; the pH of compositions B, D, F, H, and J was 7.7. It was noted that slightly more Mg diparecoxib remained in solution for the compositions prepared with $MgSO_4$. Overall, Composition G was selected as the composition to pursue further.

Table VI. Mg diparecoxib compositions

Composition	Redispersability ~48 h[a]	Sedimentation volume (mL)		Absorbance (at 245 nm)[d]	Dose Accuracy (%)[c]
		~48 h[b]	~3 min[b]		
A	15, 12	~0.9	~2.0	0.364	81.9
B	13, 12	~0.8	~1.5	0.483	95.4
C	12, 14	~0.9	~2.0	0.356	86.8
D	11, 10	~1.0	~2.7	0.431	95.8
E	18, 21	~0.6	~4.7	0.422	92.5
F	13, 16	~0.7	~4.7	0.477	99.3
G	11, 12	~0.9	~1.7	0.322	98.9
H	13, 12	~0.8	~1.5	0.465	87.5
I	14, 15	~1.0	~2.0	0.458	107.8
J	12, 13	~1.2	~3.6	0.678	97.1

a: number of inversions required to resuspend.
b: volume of 5 mL suspension.
c: with 27 gauge needle, 1cc syringe.
d: > 48 h in supernatant (100x dilution).

Example 6: Pharmacokinetic study of Mg diparecoxib, parecoxib FA, and

valdecoxib compositions in dogs

[00116] The suspensions described in Example 4 were injected in dogs and serum levels of valdecoxib were measured at the times indicated in Table VII and Figure 8.

Table VII

Time (h)	Average Valdecoxib Plasma Level (ng/mL) [n = 3 dogs]		
	Valdecoxib	parecoxib FA	Mg diparecoxib
0.000	0.0	0.0	0.0
0.167	54.4	18.6	14.2
0.500	107.0	228.0	94.8
1.000	139.0	582.0	180.0
2.000	192.0	673.0	348.0
3.000	187.0	323.0	404.0
6.000	95.4	121.0	168.0
12.000	51.2	50.8	84.8
24.000	70.4	36.1	99.4
36.000	30.9	8.9	26.6
48.000	55.2	4.1	39.7
60.000	20.7	0.5	12.5
72.000	46.4	0.0	14.6
84.000	18.5	0.0	1.4
96.000	45.2	0.0	0.8
108.000	12.9	0.0	0.0
120.000	17.5	0.0	0.0

[00117] When the data from this same study was subjected to deconvolution and expressed as cumulative input rate, it can be seen (Figure 9) that Mg diparecoxib has a linear rate of release for at least 100 h. This is in stark contrast to valdecoxib and parecoxib FA which show that after about 25 h and 75 h respectively, little or no additional valdecoxib is released into the blood. This is a surprising and unexpected result in view of the *in vitro* solubilization data of Figure 1 and Table III that showed near maximal solubilization of Mg diparecoxib by 20 h and roughly linear solubilization for valdecoxib from the period between 1 h and 89 h. Moreover, *in vitro* solubilzation of Na parecoxib showed a linear profile, but at a rate nearly 1/10th that of Mg diparecoxib.

Example 7: Pharmacokinetic study of Mg diparecoxib composition in dogs

[00118] The objectives were to scale up the selected Mg diparecoxib composition to 1 L scale and manufacture it with aseptic technique for a

pharmacokinetic study in dogs. A batch of approx 1 L of Mg diparecoxib was manufactured and filled in depyrogenated USP Type-I glass vials. The parecoxib salt concentration was equivalent to approx 40 mg/mL parecoxib FA. Physico-chemical testing was conducted after manufacture (T=0 timepoint). The composition and a summary of the characterization results is provided in Table VIII. The composition had almost 99% of the parecoxib in suspension form, with an average particle size of approx 40 µm. The suspension was redispersable and syringeable, and also passed tests for sterility and endotoxin.

Table VIII. Characterization of 1 L Batch of Mg diparecoxib

Composition	40 mg/mL Mg diparecoxib 10 mM Tris HCl 5% Mannitol $MgCl_2$ ~5mM NaCl ~100mM[a]
Batch Size	1000 mL
Appearance	white homogenous suspension when mixed
Redispersability	six vial inversions
Syringeability with 23 gauge needle and 1cc syringe	Pass[b]
Average Particle Size by Horiba Sizer (µm)	Estimated at ~40 µm; ~20 µm with 1 min sonication
Total Content by HPLC (%)	103.3 ± 0.8
Supernatant Content (HPLC)	0.48 mg/mL
Test of Sterility	Pass
Endotoxin	Pass
a: formed *in situ* by addition of $MgCl_2$ to Na parecoxib b: also passed with 27 gauge needle	

[00119] Composition vials were also stored at different temperature conditions for an informal stability evaluation. The analytical results indicated that the composition was stable at room temperature for at least 4 weeks.

[00120] The composition was successfully administered to dogs by intramuscular injection. Plasma levels of parecoxib and its active metabolite valdecoxib were monitored up to 4 days. Significant plasma concentrations of valdecoxib were observed for at least 3 days from the Mg diparecoxib suspension composition as shown in Figure 10. For comparison, a simulated pharmacokinetic profile from an equivalent dose of Na parecoxib given intravenously is also shown.

Example 8: Simulated human plasma concentration – time profiles for Mg diparecoxib

[00121] Human plasma concentration of valdecoxib were simulated based upon dog pharmacokinetic analyses. Similar absorption rate for humans as observed in dogs. If absorption is strictly blood / plasma flow dependent, plasma levels may be 10-50% lower. The half life of valdecoxib is ~1.4 h in dogs versus ~7.4 h in humans. The minimum therapeutic concentration of valdecoxib is approx 50 ng/mL in humans (from PK studies with oral Valdecoxib). Such simulation is shown in Figure 11.